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Case–Control Study on Impact of the Telomerase Reverse Transcriptase Gene Polymorphism and Additional Single Nucleotide Polymorphism (SNP)– SNP Interaction on Non-Small Cell Lung Cancers Risk in Chinese Han Population

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Aims: To investigate the impact of telomerase reverse transcriptase (TERT) gene polymorphism and additional SNP–SNP interaction on non-small cell lung cancer (NSCLC) risk in Chinese population. *Methods:* A total of 828 participants (526 males, 302 females), with a mean age of 71.3 ± 15.7 years old, were selected, including 410 NSCLC patients and 418 normal participants. Logistic regression was performed to investigate association between single nucleotide polymorphism (SNP) and NSCLC risk. Generalized multifactor dimensionality reduction (GMDR) was used to analysis the interaction among four SNPs. *Results:* Non-small cell lung cancer risk was significantly higher in carriers of G allele of the **rs2736100** polymorphism than those with TT (TG + GG vs. TT, adjusted OR (95%CI = **1.68 (1.28–2.07)**. In addition, we also found that NSCLC risk was also significantly higher in carriers of A allele of the **rs2736098** polymorphism than those with GG (GA + AA vs. GG, adjusted OR (95%CI) = **1.52 (1.19–1.93)**. GMDR analysis indicated that there was a significant two-locus model ($P = 0.0100$) involving **rs2736098 and rs2736100**, indicating a potential gene–gene interaction between **rs2736098 and rs2736100**. Overall, the two-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 62.17%. We found that patients with GA or AA of **rs2736098** and TG or GG of **rs2736100** genotype have the highest NSCLC risk, compared to patients with GG of **rs2736098** and TT of **rs2736100** genotype, OR (95%CI) was 2.52 (1.68–3.68), after covariates adjustment. *Conclusions:* Minor allele of **rs2736098 and rs2736100** in TERT gene and interaction between the two SNP were associated with increased risk of NSCLC risk. J. Clin. Lab. Anal. **30**:1071–1077, 2016.

Key words: interaction; non-small cell lung cancer; polymorphism; single nucleotide polymorphism; telomerase reverse transcriptase

INTRODUCTION

Lung cancer was the leading cause of cancer deaths in males and the second leading cause of cancer deaths in females. The International Agency for Research on Cancer (IARC) estimated that more than 1,400,000 patients die from lung cancer annually throughout the world (1). Based on the tissue origin, lung cancer can be classified into adenocarcinoma, squamous cell carcinoma, and small cell lung cancer (SCLC), where in adenocarcinoma and squamous cell carcinoma are also known as non-small cell lung cancer (NSCLC), taking 80% mortality

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of lung cancer (2,3). Tobacco smoking is the major cause attributing to lung cancer, but gene polymorphism and additional SNP–SNP interaction has been considered a definitive way of lung cancer development. Related to genetic susceptibility to lung cancer, a number of loci have been identified in genome-wide association studies (GWAS). Recently published studies (4,5) indicate that one such genetic region associated with lung cancer risk is the short arm of chromosome 5 near CLPTM1L and including SLC6A19, SLC6A18, telomerase reverse transcriptase (TERT), and SLC6A3. Among these loci, TERT gene was consistently associated with NSCLC in multiple GWAS and replication studies (6–9).

Telomerase reverse transcriptase, the reverse transcriptase component of telomerase, plays critical roles in maintenance of telomere, chromosome stability, and ultimately preventing normal cell malignance (10). Aside from the telomere elongation, many biological functions of TERT have been shown to be associated with tumorigenesis and tumor progression. Although some population-based studies have reported the association between TERT gene polymorphism and NSCLC in different populations, however, less study focused on the impact of SNP–SNP interaction on NSCLC risk was conducted, particularly in Chinese population. So the aim of this study was to investigate the impact of TERT gene polymorphism and additional SNP–SNP interaction on NSCLC risk in Chinese population.

MATERIALS AND METHODS

Participants

This was a case–control study for Chinese population. Participants were consecutively recruited between March 2009 and September 2014 from The Eastern Hospital of the First Affiliated Hospital, Sun Yat-sen University. Patients were diagnosed and sample histology was reviewed according to the World Health Organization tumor classification criteria (11). A total of 410 NSCLC patients were included in the study, controls were matched by sex, age, and ethnic background, and normal controls with family history of NSCLC were excluded. At last, a total of 828 participants (526 males, 302 females), with a mean age of 71.3 ± 15.7 years old, were selected, including 410 NSCLC patients and 418 normal participants (Fig. 1). Informed consent was obtained from all participants.

Body measurements

A standard questionnaire administered by trained staffs and we can obtained some data including demographic information, lifestyle risk factors, and family history of NSCLC for all participants. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. WC was measured two times at 1 cm above the umbilicus at minimal respiration by trained observers; the mean of the two waist circumference (WC) measurements was utilized in the analysis. Cigarette smokers were those who self-reported smoking cigarettes at least once a day for 1 year or more. Alcohol consumption was expressed as the sum of milliliters of alcohol per week from wine, beer, and spirits. Body weight, height, and WC were measured. Blood samples were collected in the morning after at least 8 hr of fasting. All plasma and serum samples were frozen at −80°C until laboratory testing. Plasma glucose was measured using an oxidase enzymatic method. The concentrations of HDL cholesterol and triglycerides were assessed enzymatically using an automatic biochemistry analyzer (Hitachi Inc., Tokyo, Japan) and commercial reagents. All analysis was performed by the same lab.

Genomic DNA extraction and genotyping

We selected single nucleotide polymorphisms (SNPs) within the TERT gene including: (a) those which have been reported to have associations with NSCLC risk previously; (b) those reported to have associations with the other cancers; and (c) minor allele frequency (MAF) >2%. A total of four SNPs within the TERT gene were selected in the study: **rs2736098, rs2736100,** rs2853669, and rs2853677. All SNPs were detected by Taqman fluorescence probe (Shanghai Biological Engineering Technology Co., Ltd., Shanghai, China). Probe sequences of all SNPs were shown in Table 1. ABI Prism7000 software (Applied Biosystems, Carlsbad, CA) and allelic discrimination procedure was used for the genotyping of fore-mentioned four SNPs. Genomic DNA from participants was extracted from EDTA-treated whole blood, using the DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. A 25-μl reaction mixture including 1.50 μl SNP Genotyping Assays (20×), 12.25 μl Genotying Master Mix (2×), 25 ng DNA, and the conditions were as follows: initial denaturation for 10 min and 95°C, denaturation for 15 sec and 93°C, annealing and extension for 92 sec and 65°C, 60 cycles.

Statistical analysis

The mean and standard deviation (SD) were calculated for normally distributed continuous variables, which were compared using Student's *t*-test, and

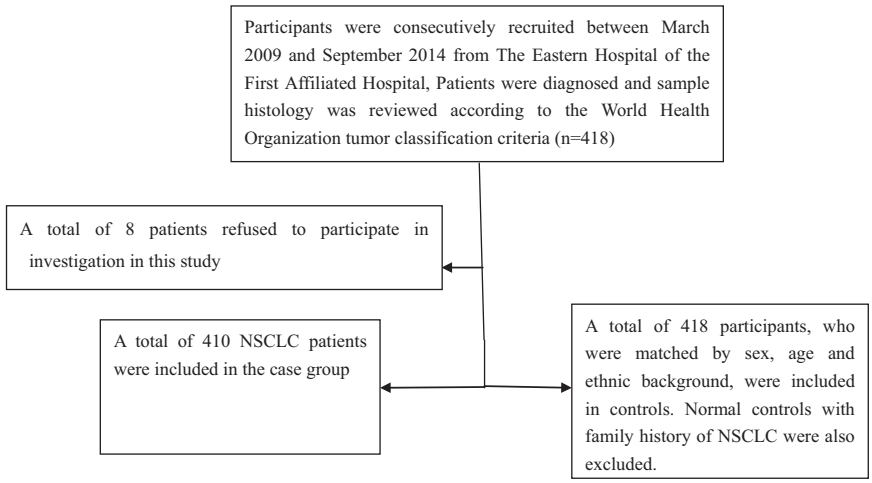

Fig. 1. A flowchart on study population selection and exclusion.

TABLE 1. Description and Probe Sequence for four Single Nucleotide Polymorphisms (SNPs) used for Taqman Fluorescence Probe Analysis

SNP ID	Chromosome	Functional consequence	Nucleotide substitution	Probe sequence
rs2736100	5:1286401	Intron variant, upstream variant 2KB, utr variant 5 prime	T > G	5'- ATTGTTTTCCGTGTTGAGTGTTTCT[T/G] TAGCTTTGCCCCCGCCCTGCTTTTC-3'
rs2736098	5:1293971	Synonymous codon	A > G	5'- CATCCGTGGGCCGCCAGCACCACGC[A/G] GGCCCCCCATCCACATCGCGGCCAC-3'
rs2853669	5:1295234	Upstream variant 2KB	T > C	5'- GGGCACAGACGCCCAGGACCGCGCT[C/T] CCCACGTGGCGGAGGGACTGGGGAC-3'
rs2853677	5:1287079	Intron variant, upstream variant 2KB	A > G	5'-TCATTTTTTTGTCACTAGAGACCCG[A/G] CTGGTGCACTCTGATTCTCCACTTG-3'

percentages were calculated for categorical variables, which were compared using χ^2 test. Hardy–Weinberg equilibrium (HWE) was performed by using SNPStats (available online at http://bioinfo.iconcologia.net/SNPstats). Logistic regression was performed to investigate association between SNP and NSCLC risk. Generalized multifactor dimensionality reduction (GMDR) (12) was used to analyse the interaction among four SNPs; cross-validation consistency, the testing balanced accuracy, and the sign test, to assess each selected interaction, were calculated. The cross-validation consistency score is a measure of the degree of consistency with which the selected interaction is identified as the best model among all possibilities considered. The testing balanced accuracy is a measure of the degree to which the interaction accurately predicts case–control status with scores between 0.50 (indicating that the model predicts no better than chance) and 1.00 (indicating perfect prediction). Finally, a sign test or a permutation test (providing empirical *P*-values) for prediction accuracy can be used to measure the significance of an identified model.

RESULTS

A total of 828 participants (526 males, 302 females), with a mean age of 71.3 ± 15.7 years old, were selected, including 410 NSCLC patients and 418 normal participants. Participants' characteristics stratified by cases and controls are shown in Table 2. The distribution of family history of lung cancer was significantly different between cases and controls, and family history of lung cancer rate was higher in cases than that in controls. The mean of WC and BMI were significantly different between cases and controls, the mean of WC and BMI were higher in controls than that in cases.

All genotypes were distributed according to Hardy–Weinberg equilibrium in controls (all *P*-values more than 0.05). The frequencies for G allele of **rs2736100**

TABLE 2. General Characteristics of 828 Study Participants in Case and Control Group

Variables	Case group (n = 410)	Normal group (n = 418)	P-values
Age (year)	70.8 ± 16.7	71.9 ± 16.1	0.335
Males, N (%)	270 (65.8)	256 (61.2)	0.192
Smoke, N (%)	221 (53.9)	208(49.8)	0.261
Alcohol consumption, N (%)	189 (46.1)	176 (42.1)	0.277
WC (cm)	86.2 ± 18.8	89.7 ± 18.4	0.007
BMI (kg/m^2)	23.1 ± 9.0	24.6 ± 9.2	0.018
TC (mmol/l)	4.5 ± 0.9	4.4 ± 0.8	0.091
HDL (mmol/l)	1.26 ± 0.65	1.30 ± 0.63	0.369
Family history of lung cancer N (%)	140 (34.1)	107 (25.6)	0.009

Means ± standard deviation for age, WC, BMI, TC, and HDL-C.
TC, total cholesterol; HDL, high-density lipoprotein; WC, waist circumference; BMI, body mass index.

and A allele of **rs2736098** of TERT gene were significantly higher in NSCLC cases than that in controls (19.5% vs. 28.7% and 20.6% vs. 30.5%). Logistic regression analysis showed that NSCLC risk was significantly higher in carriers of G allele of the **rs2736100** polymorphism than those with TT (TG + GG vs. TT, adjusted OR (95%CI) = **1.68 (1.28–2.07)**. In addition, we also found NSCLC risk was also significantly higher in carriers of A allele of the **rs2736098** polymorphism than those with GG (GA + AA vs. GG, adjusted OR (95%CI) = **1.52 (1.19–1.93)**. However, we did not find any significant association between the others SNP and NSCLC risk (Table 3).

Generalized multifactor dimensionality reduction analysis was used to investigate the impact of the interaction among four SNPs on NSCLC risk. Table 4 summarizes the results obtained from GMDR analysis for SNP–SNP interaction, we found that there was a significant two-locus model (P = 0.0100) involving **rs2736098 and rs2736100**, indicating a potential gene–gene interaction between **rs2736098 and rs2736100**.

TABLE 3. Genotype and Allele Frequencies of four Single Nucleotide Polymorphisms (SNPs) between Case and Control Group

SNP	Genotypes and alleles	Frequencies N (%)		OR(95%CI)*	H–W test for controls
		Control (n = 410)	Case (n = 418)		
rs2736100	TT	268 (65.4)	216 (51.7)	1.00	0.452
	TG	124 (30.2)	164 (39.2)	1.54 (1.24–1.86)	
	GG	18 (4.4)	38 (9.1)	2.02 (1.46–2.93)	
	TG+GG	142 (34.6)	202 (48.3)	1.68 (1.28–2.07)	
	T	660 (80.5)	596 (71.3)		
	G	160 (19.5)	240 (28.7)		
rs2736098	GG	264 (64.4)	210 (50.2)	1.00	0.092
	GA	123 (30.0)	161 (38.5)	1.41 (1.15–1.73)	
	AA	23 (5.6)	47 (11.2)	1.88 (1.29–2.57)	
	GA+AA	146 (35.6)	208 (49.8)	1.52 (1.19–1.93)	
	G	651 (79.4)	581 (69.5)		
	A	169 (20.6)	255 (30.5)		
rs2853669	TT	235 (57.3)	215 (51.4)	1.00	0.249
	TC	145 (35.4)	162 (38.8)	1.15 (0.88–1.51)	
	CC	30 (7.3)	41 (9.8)	1.19 (0.83–1.68)	
	TC+CC	175 (42.7)	203 (48.6)	1.16 (0.86–1.56)	
	T	615 (75.0)	592 (70.8)		
	C	205 (25.0)	244 (29.2)		
rs2853677	AA	239 (58.3)	220 (52.6)	1.00	0.989
	AG	148 (36.1)	165 (39.5)	1.10 (0.84–1.46)	
	GG	23 (5.6)	33 (7.9)	1.14 (0.81–1.61)	
	AA+GG	171 (41.7)	198 (47.4)	1.11 (0.83–1.49)	
	A	626 (76.3)	605 (72.4)		
	G	194 (23.7)	231 (27.6)		

*Adjusted for gender, age, smoking and alcohol status, BMI, and WC.

TABLE 4. Generalized Multifactor Dimensionality Reduction Analysis on the Best Gene–Gene Interaction Models

Locus no.	Best combination	Cross-validation consistency	Testing accuracy	*P*-values *
2	**rs2736098 rs2736100**	10/10	0.6217	0.0100
3	**rs2736098 rs2736100** rs2853669	9/10	0.5590	0.0547
4	**rs2736098 rs2736100** rs2853669 rs2853677	8/10	0.5399	0.1719

*Adjusted for gender, age, smoking and alcohol status, BMI, and WC.

Overall, the two-locus models had a cross-validation consistency of 10 of 10, and had the testing accuracy of 62.17%.

In order to obtain the odds ratios and 95%CI for the joint effects of **rs2736098 and rs2736100** on NSCLC risk, we conducted interaction analysis between the two SNP by using logistic regression. We found that participants with GA or AA of **rs2736098** and TG or GG of **rs2736100** genotype have the highest NSCLC risk, compared to participants with GG of **rs2736098** and TT of **rs2736100** genotype, OR (95% CI) was 2.52(1.68–3.68), after covariates adjustment (Table 5).

DISCUSSION

In this study, we investigated the impact of TERT gene polymorphism on NSCLC risk. We found that the frequencies for G allele of **rs2736100 and A** allele of **rs2736098** in TERT gene were significantly higher in NSCLC cases (19.5% vs. 28.7% and 20.6% vs. 30.5%) than that in controls, and NSCLC risk was significantly higher in carriers of G allele of the **rs2736100** polymorphism than those with TT, and significantly higher in carriers of A allele of the **rs2736098** polymorphism than those with GG. However, we did not find any significant association between the others SNP and NSCLC risk. Worldwide, cigarette smoking has been established as a primarily environmental risk factor of lung cancer, but only a fraction of smokers develop lung cancer during their lifetime. In contrast, there are a significant proportion of lung cancer cases with no history of smoking (13,14). Related to genetic susceptibility to lung cancer, a number of loci have been identified in genome-wide association studies (GWAS). Recently published studies (4,5) indicate that one such genetic region associated with lung cancer risk is the short arm of chromosome 5 near CLPTM1L and including TERT gene, which was consistently associated with NSCLC in multiple GWAS and replication studies (6–9). Some population-based studies have focused on the association between TERT gene polymorphism and NSCLC risk in different populations (15–17,22,23). In a study by Zhao et al. (15), they investigated the association between genetic variants of TERT rs2736098 and CLPTM1L rs401681 and lung cancer, with a total of 980 Chinese cases included. The results suggested that TT genotype of TERT s2736098 was significantly associated with an increased risk of lung cancer, especially lung adenocarcinoma and small cell carcinoma. In an investigation by Zhong et al. (16), three polymorphisms TERT-rs2853669, rs2736108, and CLPTM1L-rs31490 showed significant association with increased risk of lung cancer, especially in NSCLC. A meta-analysis conducted by Wu et al. (17) suggested that the rs2736098 polymorphism may contribute to the risk of lung cancer, especially adenocarcinoma, in the Chinese population. In addition, the current meta-analysis indicates that this genetic variant is only weakly associated with overall cancer risk. However, the rs2736098 polymorphism may affect individual susceptibility to lung and bladder cancer.

TABLE 5. Logistic Regression on Interaction between rs2736098 and **rs2736100**

rs2736098	rs2736100	OR (95% CI)*	*P*-values
GG	TT	1.00	–
GA or AA	TT	1.28 (1.10–1.57)	0.001
GG	TG or GG	1.53 (1.18–2.09)	<0.001
GA or AA	TG or GG	2.52 (1.68–3.68)	<0.001

*Adjusted for gender, age, smoking and alcohol status, BMI, and WC.

Telomerase reverse transcriptase rs2736100 was another SNP which was more studied in previously studies, and the C allele of rs2736100 has been associated with increased risk for multiple cancers in several GWAS and follow-up meta-analyses (7,18–20). Jin et al. (21) indicated that rs2736100C allele in TERT gene was associated with a significantly increased risk of NSCLC with adjusted odds ratios of 1.26 [95% confidence interval (CI) 5 1.05–1.51] and 1.31 (95% CI 5 1.04–1.66) for one or two copies of the variant C allele, respectively, which was consistent with results in a study by Zhao et al. (15). Wei et al. (22) suggested that rs2736100 may, at least in part, play a causal role in conferring lung cancer risk. The results of current study were all consistent with these studies. TERT rs2853677 was a SNP which was not well studied

previously. Van Dyke et al. (23) conducted a study and suggested that TERT rs2853677 minor allele was associated with increased NSCLC risk both in Caucasian and African Americans. However, in current, we did not find any association between rs2853677 minor allele and NSCLC risk.

Non-small cell lung cancer risk was influenced by many genetic factors and many SNPS, so it was necessary to investigate the impact of SNP–SNP interaction on NSCLC risk. In the GMDR analysis, we found that there was a significant SNP–SNP interaction between **rs2736098 and rs2736100,** and participants with GA or AA of **rs2736098** and TG or GG of **rs2736100** genotype have the highest NSCLC risk, compared to participants with GG of **rs2736098** and TT of **rs2736100** genotype. To our knowledge this was the first study for investigating SNP–SNP interaction between **rs2736098 and rs2736100** on NSCLC risk in Chinese population. The results of current study suggested that **rs2736100** genetic variants may modify and influence the risk of NSCLC in an **rs2736098**-dependent relation.

Several limitations of this study should be considered. Firstly, limited number of SNP in TERT gene was chosen in this study. More SNPs should be included in the further studies, not only interaction with SNPs in the same gene but also interaction with SNPs in different genes. Secondly, gene–environment interaction should be investigated in the future, including interaction with unhealthy lifestyle, such as smoking and so on. Thirdly, the size of the sample should be larger, although the sample size in this study met requirement, in addition, this association should be verified in different races.

In conclusion, the results of current study indicated that G allele of the rs2736100 and A allele of the rs2736098 were associated with increased NSCLC risk. In addition, we also found a significant SNP–SNP interaction between rs2736098 and rs2736100, participants with GA or AA of rs2736098 and TG or GG of rs2736100 genotype have the highest NSCLC risk.

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